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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,840	03/13/2001	Gregory R. Mundy	10274-034001	4957

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,840	MUNDY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,9,31,32,40 and 42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,9,31,32,40 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/26/05 has been entered.

2. Claims 1-2, 4-5, 9, 31-32, 40 and 42-44 are pending and under consideration in this application.

3. The declaration filed under 37 CFR1.131 by Drs. Gregory Mundy and Toshiyuki Yoneda on 5/26/05 is sufficient to antedating Van Zaanen et al reference.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-2, 4, 5, 9, 31-32 and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,495,525 in view WO 95/19790.

The `525 patent teaches a method for treating multiple myeloma in a mammal comprising administering to a compounds which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V (see patented claim 9, col., 30, and col., 4, line 21-40 in particular). The `525 patent further teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo (see col., lines 57-58 in particular). Additionally, the `525 patent teaches that the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin. These compounds are

useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. These compounds are useful for inhibition, prevention and suppression of VLA-4-mediated cell adhesion and pathologies associated with that adhesion such as multiple myeloma (col., 2, line 64 through col., 3, line 21 and patented claim 9 in particular). Finally, the `525 patent teaches the composition is employed in dosage range from about 0.001-25 mg/kg (see col., 10, lines 60-63 in particular).

The claimed invention differs from the reference teachings only by the recitation that the method comprises the administration of anti-alpha4 antibody in claim 1, anti-alpha4/beta1 (VLA-4) antibody in claim 2, that the antibody antagonizes the interaction of both VLA-4 and alpha4beta7 with their respective alpha4 ligands in claim 5, the antibody or fragment thereof is selected from the group consisting of a human antibody, a chimeric antibody, a humanized antibody and an antigen-binding Fab, Fab', F(ab')2 or F(v) fragment of a human, chimeric or humanized antibody in claim 5, wherein the antibody or antigen binding fragment thereof is a human antibody or antigen binding fragment thereof or a humanized antibody or antigen binding fragment thereof in claims 31, 32 and 40, wherein the antibody or antigen-binding fragment thereof is a monoclonal antibody in claim 42, wherein the anti-VLA-4 antibody or antigen-binding fragment thereof binds the alpha chain of VLA-4 in claim 43, wherein the anti-VLA-4 antibody or antigen-binding fragment thereof is a B epitope specific anti-VLA-4 antibody or antigen-binding fragment thereof in claim 44.

The WO `790 publication teaches a method of treating central nervous system in patient comprising administering to the patient a composition comprising humanized MAb 21.6 (i.e., anti-alpha4 antibody) to block α4-dependent interactions of the VLA-4 receptor (see page 24, under Methods of Treatment and page 25, lines 12-15 in particular). Also, antibodies against the VLA-4 receptor have been tested for their anti-inflammatory potential both in vitro and in vivo in animal models. These experiments identify anti-VLA-4 antibodies as potentially useful therapeutic agents for treating MS and other inflammatory disease and disorders (see page 2, lines 14-28 in particular). Furthermore, the `790 publication teaches a binding fragment of the humanized antibody (see page 21, lines 15-22 in particular). The fragments exhibit specific binding to the VLA-4 antigen, wherein humanized antibody fragments include separate heavy chains, light chains Fab, Fab', $F(ab')_2$, Fabc, and Fv (see published claim 17 and page 21, lines 14-22 in particular). In addition, the `790 publication teaches that chimeric light and heavy chains were constructed for the mouse 21.6 $V_L$ and $V_H$ regions (see page 30, line 35 through page 32, line 13 and page 41, lines 19-21 in particular). The `790 publication further teaches chimeric and mouse or human 21.6 antibody and anti-VLA-4 antibody, L25 (i.e., monoclonal antibody) (see page 5, lines 1-3, figure 4 and Figures 13 and 14 in particular). Furthermore the `790 publication teaches humanized immunoglobulins or antibodies specific for the alpha-4 subunit of VLA-4 (see page 11, lines 30-32 in particular). Finally, the `790 publication teaches that humanized anti-VLA-4 antibodies demonstrate a strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response (see page 3, lines 23-27 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the compound which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V taught by the `525 patent with mouse MAb or humanized anti-VLA-4 antibodies such as humanized MAb 21.6 (i.e., anti-alpha4 antibody) or antigen binding fragments thereof that blocks α4-dependent interactions of the VLA-4 receptor taught by the WO `790 publication in a method for treating MM as taught by the `525 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the `525 suggested the substitution implicitly since the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin with antibodies to VLA-4. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. Further, because anti-VLA-4 antibodies are used to block α4-dependent interactions of the VLA-4 receptor which are potentially useful therapeutic agents for treating MS and other inflammatory disease and disorders as taught by the WO `790 publication. Further because humanized anti-VLA-4 antibodies demonstrate a strong affinity for the VLA-4 receptor, while exhibiting little, if any, human-antimouse response as taught by the `790 publication.

Claim 44 is included because the anti-VLA-4 antibody is a function blocking antibody and therefore would the reference antibodies are a B epitope specific.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 5/26/05, have been fully considered, but have not been found persuasive.

Applicant characterizes the rejection as following: Lee discloses the use of a small molecue VLA-4 inhibitor (oMePUPA-V) to treat animal models of Pulmonary inflammation and delayed type hypersensitivity. Further Applicant submits that lee suggests that the small molecule inhibitor could also be used to teat "VLA-4-mediated cell adhesion and pathologies associated with the adhesion, such as inflammation and immune reactions" and lists 20 specific disorders within the class. Lobb and Kamata disclosse various anti-VLA-4 antibodies but do not relate to treatment of multiple myeloma. Applicant disagrees with the Examiner's conclusion that one of ordinary skill in the art would have been motivated to substitute an anti-VLA-4 antibody for 0MePUPA-V for the following reasons.

First, Applicants not that the disclosure in Lee that anti-VLA-4 antibodies have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo appears in background. Moreover, Applicants notes that Lee discloses experiments that treat animal models of pulmonary inflammation and delayed type hypersensitivity. Further Applicants note that Lee lists a broad range of other immune and inflammatory diseases that can be treated with oMePUPA-V and also lists MM and tumor metastasis. MM is a type of cancer that develops in a subset of white blood cells but it is not an immune or inflammatory disorder per se, unlike the other disorders listed in Lee or the disorders treated in the in vivo examples in lee. There is no motivation to select MM from this long list in Lee to treat with an antibody. Applicants contends that a skilled artisan would certainly not be motivated to use an antibody therapeutic to treat a neoplasm base on Lee's data showing that a small molecule drug against a target can be use to treat a disorder related to inflammation, or more particularly, to a hypersensitivity-type inflammatory response. Applicant contends that treating neoplasms with antibodies is a completely different area of medicine than treating immune-or inflammatory-mediated diseases with small molecule drugs. Applicant concludes that one of ordinary skill in the art would not have been motivated to use an anti-VLA-4 antibody to treat MM, based on the references argued by the Examiner.

However, the examiner notes that by statute, a U.S. patent is presumed to be valid and claims are presumed to be enabled. Regarding the motivation, Applicant argues that there is absolutely no motivation to select MM from this long list in Lee to treat with an antibody. However, the `525 patent teaches and claims method of treating MM (see claim 9, in particular). Given the teachings of the `525 patent that the small molecule and anti-VLA-4 antibodies are capable of inhibiting VLA-4 mediated cell adhesion, one of ordinary skill in the art at the time the invention was made would have been motivated to substitute oMEPUPA-V with anti-VLA-4 antibodies.

Applicants further argues that one of skill in the art would have no reasonable expectation of success, based on Lee to use an anti-VLA-4 antibody to treat MM. Applicant points to that Declaration under 37 C.F.R. 132 of Dr. Blake Pepinsky , submitted with the Amendment filed 1/30/04, that antibodies are completely different than small molecules: First, antibodies as a class of agent differ greatly in terms of structure from small molecules. For example, antibodies are vastly different in size than small molecule drugs such as oMePUPA-V. This structural difference means that antibodies work very differently. Applicants contend that they act by very different mechanisms of action. Applicant states that this is not a case where one can simply conclude that, if antibodies bind and work, and small molecules bind and work, then the two are interchangeable. Applicant points to Pepinsky Declaration, due to its small size, a small molecule works in very different ways. A small molecule drug is typically directed to a "pocket" or specific docking site on the target molecule, where it may act as either an agonist or ant antagonist. In contrast, antibodies are large moelcuels that although they bind to a particular epitope, their structural attribute means they work in very different easy than small molecules, and effectively cover a large surface area and thereby act to block a biological pathway through stearic hindrance, as opposed to binding a specific active site or pocket. Applicant further draws the examiner's attention to Pepinsky declaration which states that oMePUPA-V binds at the ligand binding site and therefore may act as an agonist. In contrast, none of the existing anti-α

integrin antibodies bind directly at the ligand binding site. Applicant concludes that a skilled practitioner would not have believed that oMePUPA-V, which differs greatly in structure from a small molecule, would be interchangeable with an anti-α4 integrin antibody.

Examiner realizes and appreciates the difference between the antibodies and the small molecule drugs mechanism of action, however, the issue is the obviousness for one ordinary skill in the art at the time of the invention was made to use the VLA-4 inhibitor to treat MM. The `525 patent provides a method for treating multiple myeloma in a mammal comprising administering to a compounds which are capable of inhibiting VLA-4 mediated cell adhesion by inhibiting the binding of ligands to that receptor such as oMePUPA-V. Additionally, the `525 patent teaches that the compounds of the invention are inhibitors of VLA-4 integrin thereby blocking the binding of VLA-4 to its various ligand, such as VCAM-1 and regions of fibronectin. These compounds are useful in inhibiting cell adhesion processes, including cell activation, migration, proliferation and differentiation. The `525 patent further teaches anti-VLA-4 monoclonal antibodies which have been shown to inhibit VLA-4 dependent adhesion interactions both in vitro and in vivo. Therefore, the `525 suggested that suggests that anti-VLA-4 monoclonal antibodies antagonist that mimic small molecule drugs can also be effective therapeutics. Furthermore, obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousnes. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). See MPEP 2143.02.

Applicants continue to argue that antibodies have a structure referred to as an Fc receptor, the small molecules of the cited art do not have this structure. Applicants conclude that in contrast to oMePUPA-V, an antibody-based therapeutic would be expected to implicate aspects of the immune response in its effect. Applicant points to Pepinsky Declaration for the binding of Fc receptors by the Fc domain of an antibody molecule provided signals that activate and recruit immune and inflammatory cells, or, alternatively, that send inhibitory signals that downregulate immunity. The implication of additional immune mechanisms with an antibody could result in completely different effect in vivo than that of oMePUPA-V. Applicant contends that even if an antibody and a small molecule were alike in all other respects, this difference in activity alone would mean they are not interchangeable. Applicant concludes that a skilled artisan would not have reasonably predicted that an anti-α4 integrin antibody, which has an Fc receptor structure would have the same effect as oMePUPA-V, which lacks such a structure, in vivo. Applicant point that such antibody-specific mechanisms are an important reason why an antibody and a small molecule would not be considered interchangeable.

However, the Examiner notes that pending claims recite antigen-binding fragments that do not require the Fc domain. Thus the antigen binding fragments of anti-α4 antibodies would result in the same effect in vivo as oMePUPA-V.

Applicant disagree with the examiner's characterization of the issue and argues that the issue is whether, based on the disclosure of the use of a small molecule to treat MM, it would have been

obvious to one of skill in the art to use an anti-VLA-4 antibody to treat MM, and not a VLA-4 inhibitor in general. Applicants have outlined , as the Examiner has realized, the differences between antibodies and small molecules. Applicant reiterate that antibodies and small molecules are different in their structures , as well as in their mechanisms of action. Applicant concludes that a skilled artisan would not have reasonably predicted that an anti-a4 integrin antibody would have the same effect as oMePUPA-V in vivo.

However, the Examiner notes that oMePUPA-V performs the identical function specified in the claim in substantially the same way of bind to VLA-4, and produces substantially the same results as the claimed anti-α4 antibodies.

Applicant submits that the activity or function of a molecule is dictated by its structure. The antibody structure allows binding to a different spectrum of targets than does the structure of the small molecule. Moreover, there is yet another structure/function difference. Anti-α integrin antibodies, as recited in the claims, have a structure that imparts a different specificity than oMePUPA-V. Applicant contends that Lee teaches that oMePUPA-V is highly specific for VLA-4 having α4β1 but does not act on α4β7 integrin. In contrast, the α4 integrin antibodies recited in the claims can bind both α4β1 and α4β7 implicating an additional integrin pathway. The broader specificity of an anti-α4 integrin, compared to oMePUPA-V, would have made it unpredictable that an anti-α4 antibody structure would have the same effect as oMePUPA-V small structure in vivo at all, much less have the same applicability across such a broad rang of disorders. Even if antibodies and small molecules were exactly alike in every other way, this difference in specificity would show they are not interchangeable.

However, the examiner notes that the oMePUPA-V, anti-α4 antibodies and the anti-VLA-4 antibodies are VLA-4 inhibitors. The anti-VLA-4 antibodies are a species of the claimed anti-alpha4 integrin antibody. Therefore, the prior art met the claimed limitation, irrespective of the broad specificity of the anti-α4 antibodies.

Finally, Applicant argues that the only side-by-side comparison of antibodies and small molecules in the cited art is in Example 3 of Lee. Applicant points that in example 3, Lee compared the use of an anti-VLA-4 antibody to the use of oMePUPA-V to treat animal models of delayed type hypersensitivity. Further, the antibody was effective, but the small molecule was not. Applicant concludes that an anti-VLA-4 antibody and oMePUP-V are not interchangeable to treat inflammatory mediated diseases.

The Examiner's position is that the `525 patent (Lee) claims are drawn to a method of treating MM with the small organic molecule, even thought the small organic molecule has no efficacy in the delayed type hypersensitivity model. The antibody would always work, irrespective of whether the small organic molecule inhibits the delayed type hypersensitivity or not.

Applicant responses to the Examiner's previous statement that the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Applicant points that the examiner is assuming that the two mechanisms give the same

result. Applicant argues in conjunction with Pepinsky Declaration, that a small molecule might act as an agonist. Further, the reference is not an anticipatory reference, that merely elucidating mechanism would not confer patentablility. Applicant contends that the issue here is different. Applicant contends that the art teaches one structure, while the claims are limited to the use of a very different structure. Applicant argues that the mechanism helps explain why the differences in structure are relevant. Applicant concludes that the PTO is misapplying a novelty analysis. Applicant further contends that the fact that two structurally different molecules work in very different ways and can give very different results, is certainly relevant to the issue of interchangeability. This is an obviousness rejection of the use of an antibody over the use of a structurally and functionally distinct small molecule.

However, the examiner notes in this instant case the prior art of `525 patent teaches that the small molecule of oMePUPA-V is an inhibitor of VLA-4 (i.e., antagonist) (see the patent title in particular), the ordinary skilled in the art would not expect the inhibitor to act as agonist to give very different results. The anti-VLA-4 and anti-α4 antibodies are also inhibitors of VLA-4, thus the small molecule and the anti-VLA-4 antibodies share same mechanism of action by inhibiting the VLA-4 receptor binding to its ligands. The issue Applicant is raising is in the structure of the inhibitor rather than in the mechanism of action of achieving MM treatment, since both act on the same receptor to accomplish the same end result. The examiner's position is that it is obvious to substitute one inhibitor with another known inhibitor of VLA-4 to achieve the inhibition of VLA-4 receptor to its ligands to treat MM.

6. The provisional rejection under judicially created doctrine of Obviousness-type double patenting is hereby withdrawn because copending Applicant No. 09/943,659 is now abandoned.

7. The provisional rejection under judicially created doctrine of Obviousness-type double patenting is hereby withdrawn because claims 1, 2, 4, 5, 9, 11, 12, 17, 18, 20, 21, 25, 27, 34, 35, 37 and 44 of copending Applicant No. 10/086,217 is now canceled.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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July 27, 2005

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